12-23-02

DAC

Practitioner's Docket No. 56873 (71699) *PATENT*

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of: Chris D. Constantinides
Application No.: 10/044,296 Group No.: 3737
Filed: 1/10/2002 Examiner: TBA
For: MAGNETIC RESONANCE IMAGING METHODS AND COMPOSITIONS

BOX DAC
Assistant Commissioner for Patents
Washington, D.C. 20231

EXPRESS MAIL CERTIFICATE

"Express Mail" label number EL 932684425 US
Date of Deposit DECEMBER 20, 2002

I hereby state that the following *attached* papers and or fees

1. Petition Under 37 CFR § 1.47 (in duplicate);
2. Proof of Proprietary Interest under § 1.47(f), together with Report of Invention Disclosure Form, and Executed General Power of Attorney;
3. Statement of Facts in Support of Filing on Behalf of Non-Signing Inventor under 37 CFR § 1.47;
4. Details of Refusal of Non-Signing Inventor to Sign Application Papers;
5. Exhibits A-D;
6. Petition for Revival of an Application for Patent Abandoned Unintentionally under § 1.137(b) (in duplicate);
7. Completion of Filing Requirements—Nonprovisional Application (in duplicate);
8. Notice to File Missing Parts of Nonprovisional Application –Copy to be returned with response; and
9. Executed Combined Declaration Power of Attorney

is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 C.F.R. section 1.10, on the date indicated above and is addressed to the Assistant Commissioner for Patents, BOX DAC, Washington, D.C. 20231.

BETH-ANN MARINO
Typed or printed name of person mailing paper or fee

Beth-Ann Marino
Signature of person mailing paper or fee

NOTE: The label number need not be placed on each page. It should, however, be placed on the first page of each separate document, such as, a new application, amendment, assignment, and transmittal letter for a fee, along with the certificate of mailing by "Express Mail" Although the label number may be on checks, such a practice is not required. In order not to deface formal drawings it is suggested that the label number be placed on the back of each formal drawing or the drawings be accompanied by a set of informal drawings on which the label number is placed.

BOS2_178868.1

UNITED STATES PATENT AND TRADEMARK OFFICE

COMMISSIONER FOR PATENTS
UNITED STATES PATENT AND TRADEMARK OFFICE
WASHINGTON, D.C. 20231
www.uspto.gov

APPLICATION NUMBER	FILING/RECEIPT DATE	FIRST NAMED APPLICANT	ATTORNEY DOCKET NUMBER
10/044,296	01/10/2002	Chris D. Constantinides	56783

CONFIRMATION NO. 6836

FORMALITIES LETTER

OC000000007529642

EDWARDS & ANGELL, LLP
Dike, Bronstein, Roberts & Cushman
IP Group
P.O. Box 9169
Boston, MA 02209

Date Mailed: 02/25/2002

NOTICE TO FILE MISSING PARTS OF NONPROVISIONAL APPLICATION

FILED UNDER 37 CFR 1.53(b)

Filing Date Granted

An application number and filing date have been accorded to this application. The item(s) indicated below, however, are missing. Applicant is given **TWO MONTHS** from the date of this Notice within which to file all required items and pay any fees required below to avoid abandonment. Extensions of time may be obtained by filing a petition accompanied by the extension fee under the provisions of 37 CFR 1.136(a).

- The statutory basic filing fee is missing.
  Applicant must submit $ **740** *to complete the basic filing fee for a non-small entity. If appropriate, applicant may make a written assertion of entitlement to small entity status and pay the small entity filing fee (37 CFR 1.27).*
- Total additional claim fee(s) for this application is $622.
  - **$342** for **19** total claims over 20.
  - **$280** for multiple dependent claim surcharge.
- The oath or declaration is missing.
  A properly signed oath or declaration in compliance with 37 CFR 1.63, identifying the application by the above Application Number and Filing Date, is required.
- To avoid abandonment, a late filing fee or oath or declaration surcharge as set forth in 37 CFR 1.16(l) of $130 for a non-small entity, must be submitted with the missing items identified in this letter.
- **The balance due by applicant is $ 1492.**

The application is informal since it does not comply with the regulations for the reason(s) indicated below.

The required item(s) identified below must be timely submitted to avoid abandonment:

- Substitute drawings in compliance with 37 CFR 1.84 because:
  - Drawings must be reasonably free from erasures and must be free from alterations, overwritings, interlineations, folds, and copy marks.
  - drawings contain excessive text. Suitable descriptive legends may be used, or may be required by the Examiner where necessary for understanding of the drawing but

should contain as few words as possible (see 37 CFR 1.84(o));

A copy of this notice MUST be returned with the reply.

Customer Service Center
Initial Patent Examination Division (703) 308-1202
PART 2 - COPY TO BE RETURNED WITH RESPONSE

The JOHNS HOPKINS UNIVERSITY School of Medicine

Confidential

Office of Technology Licensing

Report of Invention

Disclosure Form

This form is to be completed and submitted to the JHUSOM Office of Technology Licensing (OTL) by anyone who believes they have developed a new invention. The purpose of this form is to enable the OTL to evaluate whether legal protection to the invention will be sought and/or commercialization pursued. In order for this Report of Invention to be processed by OTL, it must be signed and dated by all inventors, and by the JHU Department Director for each department involved with the development of this invention. OTL can not process this report until it is complete with all necessary signatures.

INVENTION INFORMATION

Title of Invention: SODIUM (23Na) MRI FOR DETECTING MYOCARDIAL INFARCTION USING A PARAMAGNETIC CONTRAST AGENT

Lead Inventor Information: [The lead inventor is the primary contact person for OTL.]

Name of Lead Inventor: (Last, First, Middle)

CONSTANTINIDES CHRISTAKIS D

Title or Position:	Ph.D.
Department:	BIOMEDICAL ENGINEERING
Business phone:	(202) 364 0300
Business fax:	(202) 364 9910
E-mail:	cdc04@yahoo.com
Business address:	4936 RODMAN AVENUE N.W. WASHINGTON D.C. 20016.
Home phone number:	(412) 417 7349 / (813) 786 4809
Home fax number:	(357) 5 391071
Home address:	2, EVRYVIADOU STREET MONOVOLIKOS 4TH LIMASSOL 3224, CYPRUS.
Citizenship:	CYPRIOT
Social Security Number:	578 23 4646
Department(s) in which invention was developed:	RADIOLOGY
Are you an HHMI investigator?	(Yes) No (Circle one)
Are you a KKI investigator?	Yes (No) (Circle one)

OTL Internal Use Only:	DM No. 3907	TLA: LAP	Field of Use: 2B

Confidential

ADDITIONAL INVENTOR(S) [Please make copies of this table as needed.]
Name of Inventor: (Last, First, Middle)
Title or position:
Department:
Business phone:
Business fax
E-mail:
Business address:
Home phone number:
Home fax number:
Home address:
Citizenship:
Social Security Number:
Are you an HHMI investigator? Yes No (Circle one)
Are you an KKI investigator? Yes No (Circle one)

INVENTION DESCRIPTION

Describe the invention completely, using the outline given below.

1. Abstract of the Invention [Briefly describe the invention.]

Please see attached copies of abstract and manuscript.

Confidential

On a separate page(s), attach a detailed description of how to make and use the invention. The description must contain sufficient detail so that one skilled in the same discipline could reproduce the invention. Include the following as necessary:

1- data pertaining to the invention;
2- drawings or photographs illustrating the invention;
3- structural formulae if a chemical;
4- procedural steps if a process; and
5- a description of any prototype or working model;

Confidential

In general, a manuscript that has been prepared for submission to a journal will satisfy this requirement. Please see attached copies of abstract and manuscript.

5. Workable Extent/Scope
[Describe the future course of related work, and possible variations of the present invention in terms of the broadest scope expected to be operable; i.e., if a ***compound***, describe substitutions, breadth of substituents, derivatives, salts etc.; if ***DNA or another biological material***, describe modifications that are expected to be operable; if a ***machine or device***, describe operational parameters of the device or a component thereof, including alternative structures for performing the various functions of the machine or device.]

- In May of 2000 I submitted my thesis to the University library and ceased to be employed by Johns Hopkins University. The abstract, manuscript and provisional application enclosed describe the work I did that was related to my initial concept up through the date of termination of my employment by Johns Hopkins University. Such work was outside the scope of my thesis work and was pursued at my spare time.

6. References [Please list the closest and most relevant journal citations, patents, general knowledge or other public information related to the invention].

Please see attached copies of abstract and manuscript.

Confiden

2. Problem Solved [Describe the problem solved by this invention.]

Please see attached copies of abstract and manuscript.

~~* Although others have help~~

3. Novelty [Identify those elements of the invention that are new when compared to the current state of the art.]

Please see attached copies of abstract and manuscript.

4. Detailed Description of the Invention:

Confidential

RESEARCH SUPPORT INFORMATION

Indicate **ALL** contributions to the development of the invention in terms of personnel, money, materials and facilities etc.

Check each funding source that applies to this invention:

Federal Sponsor(s)-X University Funding-X Commercial Funding-___ Other-___

For each funding source, provide the following information:

Granting/Funding Source	Award/Contract Number	Title of Grant
National Institutes of Health	RO1 HL61695 (PI - Dr. P. Bottinger) *	Sodium H+ in ischemic heart disease
Whitaker Foundation	Biomedical Engineering Doctoral Fellowship (Candidate)	

Were any materials under a Materials Transfer Agreement used? (Yes) No (Circle one)

If yes, please provide the following information for each material and attach a copy of the MTA:

Source of Materials	Description of Materials
Advanced Magnetics Inc, Cambridge, MA	Superparamagnetic Iron Oxide AMI-25 at a concentration of 42 mg Fe/kg - please see copy of the signed transfer agreement

* It is important to note that the invention described herein is outside the scope of this grant, although certain costs involved in making this invention was paid for by this grant (If also was also)

Confidential

DISCLOSURES OF THE INVENTION

Check any disclosures or anticipated disclosures, either written or oral, of the Invention:

Abstract(s)-x Publication(s)-x Seminar(s)-___ Presentation(s)-x Other-___

For each disclosure, provide the following information as appropriate in the space below:

- If published, include all journal citations and attach a reprint;
- If not yet published, include a copy of the abstract or manuscript and the anticipated publication date; and
- for any other written or oral disclosure, provide the names, addresses and affiliation of anyone to whom you have disclosed the Invention and the date of any disclosure.

- Abstract presentation at the International Society of Magnetic Resonance in Medicine (ISMRM), Colorado, USA - April 1-4, 2008 - please see attached abstract.
- Journal publication to Magnetic Resonance in Medicine, submitted on January 2008 - February - please see attached.
- Oral and written disclosure to Intellectual property attorney.

COMMERCIALIZATION

List any companies who you feel may be interested in this technology or are doing similar research. Indicate how the invention complements the company's existing technology. Provide the names of any companies (and a contact person, if known) who have contacted you regarding your research related to the invention.

- Pharmaceutical Industry
- Magnetic Resonance Imaging companies (General Electric, Siemens, Philips).

Confidential

SIGNATURE PAGE

In order for the Report of Invention to be complete, and to be processed by OTL, it must be signed and dated by:

1. ***all inventors**, and*
2. *by the **JHU Department Director** for each department in which this invention was made as stated in the Invention Information Section of this form above.*

I/we, the inventors, hereby certify that the information set forth in this Report of Invention is true and complete to the best of my/our knowledge.

I/we, the inventors who are subject to The Johns Hopkins University Intellectual Property Policy and are not under an obligation to assign intellectual property rights to another party[1], hereby affirm that in consideration for The Johns Hopkins University's evaluation of commercial potential and a share of income which I/we may receive upon commercialization of my/our invention, I/we on the date of my/our signature as indicated below do hereby assign and transfer my/our entire right, title and interest in and to the invention described herein unto The Johns Hopkins University, its successors, legal representatives and assigns.

[1]HHMI and KKI Inventors are subject to a separate assignment.

Inventor Signature:	**Typed or Printed Name:** Chris D. Constantinides	**Date:** 7/30/02
Inventor Signature:	**Typed or Printed Name:**	**Date:**
Inventor Signature:	**Typed or Printed Name:**	**Date:**
Inventor Signature:	**Typed or Printed Name:**	**Date:**
Department Director Signature:	**Typed or Printed Name:** Elias A. Zerhouni	**Date:** 7/27/02
Department Director Signature:	**Typed or Printed Name:**	**Date:**
Department Director Signature:	**Typed or Printed Name:**	**Date:**
Department Director Signature:	**Typed or Printed Name:**	**Date:**

Superparamagnetic Iron Oxide MION as a Contrast Agent for Sodium MRI in Myocardial Infarction

Chris D. Constantinides, M.S.E.[†], J. Rogers, M.E.[§], D. Herzka, M.S.E.[†], F. E. Boada, Ph.D.[*], D. Bolar, B.Eng[†], D. Kraitchman, Ph.D., V.MD[#], J. Gillen, B.S.[#], P. A. Bottomley, Ph.D.[#]

[†]Dept. of Biomedical Engineering and [#]Radiology, Johns Hopkins University School of Medicine, Baltimore MD, 21205, University of Pittsburgh Medical Center, Pittsburgh PA 15213, and [§]Advanced Magnetics Inc., Cambridge, MA

Correspondence:
Chris Constantinides, PhD
Department of Radiology
University of Pittsburgh Medical Center
MR Research Center
Room B804-PUH
University of Pittsburgh Medical Center
200 Lothrop Street
Pittsburgh PA 15213
Phone: (412) 647 9700
Fax: (412) 647 9800
e-mail: constant@mrctr.upmc.edu

abbreviated title: Sodium Cardiac Imaging using a Superparamagnetic Contrast Agent.

noise ratio (SNR) losses and/or significant prolongation of the total image acquisition times. Furthermore, the similarity of the longitudinal (T_1), and fast (T_{2f}) and slow (T_{2s}) transverse relaxation times of blood and myocardium [13], preclude use of conventional inversion recovery or spin-echo techniques to null the ventricular blood signal.

The purpose of this study was to evaluate the use of MION as a constrast agent for attenuating the intense ^{23}Na MRI signal from the ventricular cavity and thereby improve the ^{23}Na MRI contrast in myocardial infarction. Specifically, we assess the variation in the blood T_1 and T_2 relaxation times with increasing MION amount and determine the optimal dose for contrast-enhanced ^{23}Na cardiac MRI in normal canine hearts *in vivo*. We demonstrate the usefulness of administered MION for detecting injury associated with acute reperfused myocardial infarction.

Materials and Methods

Phantom Studies

All MRI studies were performed with a commercially available 1.5T MRI system (*Signa, Horizon, Echo Speed, 5.7 Epic platform, GE Medical Systems, Milwaukee, WI*) equipped with braodband spectroscopy capabilities, using a 16-pole quadrature ^{23}Na birdcage coil tuned to 16.89 MHz and interfaced with a quadrature hybrid splitter. ^{23}Na MRI was performed with a three-dimensional (3D) twisted projection imaging (TPI) sequence [14] using conventional scanner hardware with gradients having a maximum amplitude of 2.2 mT/m, a maximum slew rate of 12 mT/cm/s, and with a slew rate duty cycle limit of 20%. The k-space traversals traced the surfaces of concentric cones contained inside a sphere of radius k_{max}. The desired gradient waveforms were computed from the k-space traversals and were used to encode the free induction decay.

In vitro studies were performed with a co-axial cylindrical plexiglass phantom of outer diameter 12 cm, and inner diameter 5 cm. A saline gel was prepared by mixing 4% per wt. of agarose into 500 ml of 65 mM saline in doubly de-ionized water, doped with 10mM of

copper sulphate ($CuSO_4$) and poured into the outer annular compartment of the phantom. This agarose gel provides a reasonable approximation to the ^{23}Na MRI relaxation properties of myocardial tissue. Whole blood samples were prepared by adding heparin (with 8.6 mg of sodium per ml of heparin solution) to canine blood with predetermined amounts of MION, and placed in the inner cylindrical chamber of the phantom.

Animal Preparation

Conditioned mongrel dogs weighing 25-30 kg were sedated with 10 mg/kg ketamine, 2.4 mg/kg xylanine, and 0.02 mg/kg atropine intramuscularly. An intravenous catheter was introduced, and the dog anesthetized with sodium penthothal, intubated, mechanically ventilated with 100% oxygen (tidal volume = 10-15 ml/kg, respiratory rate = 10-12 bpm) and maintained on general anesthesia with 1-2% isoflurane. Three dogs were studied as normal controls. Three dogs were subjected to a 90 to 120-minute balloon occlusion of the left anterior descending (LAD) coronary artery followed by reperfusion. A femoral artery cut-down was performed to place a 8 Fr. catheter introducer-sheath (Terumo Medical Corp., Elkton, MD) and a 7 Fr. right Judkins catheter (Cordis, Diamond Bar, CA) with a 0.014 mm guidewire and 3.5 Fr. coronary angioplasty balloon into the left anterior descending coronary artery under fluoroscopic guidance. The balloon was deflated and the occluder removed to allow reperfusion 3 to 6 hours prior to the MRI studies. MION (Advanced Magnetics Inc., Cambridge, MA) was injected intravenously in normal and in infarcted animals prior to contrast MRI. After MRI, infarcted dogs were humanely euthanized and the heart excised, sliced along the axial planes, and incubated in triphenyl-tetrazolium chloride (TTC) to identify viable from non-viable myocardium.

MRI Protocol

Dogs were positioned in the magnet in right decubitus, and an ECG-gated multislice gradient echo-transaxial ^{1}H MRI was performed with a flexible, 4-element phased array coil after autoshimming. The ^{1}H phased-array coil was then replaced by the ^{23}Na birdcage coil without

repositioning the animal. The ^{23}Na 3D TPI sequence was applied with TE=0.37 ms, TR=60 ms, 14 NEX, and a receiver bandwidth of 31.25 kHz, 1240 projections and gradient strengths up to 0.16 G/cm. To maximize detection of the short T_2 component, a 0.4 ms non-selective 90° radiofrequency (rf) excitation pulse was used. Post-contrast ^{23}Na MRI was performed (TE=0.37 ms, 5ms) at increasing MION doses in normal dogs, and in infarcted animals at the dose level of 10 mg/kg body weight (as determined from the normal dog experiments) to produce the greatest suppression of ventricular blood. The scan time per acquisition was 17 minutes.

Relaxation Measurements

To determine the variation of the ^{23}Na relaxation times of blood with the amount of MION injected, T_1 and T_2 measurements were carried out using saturation recovery (TR=60-300 ms) and spin-echo spectroscopic sequences (TE=12-35 ms) at increasing iron (Fe) concentrations ranging from 0-0.25 ml. The acquisition parameters were: 8-32 KHz, 256-512 points, NEX=96. T_{2f} and T_{2s} and image contrast were also measured from sequentially acquired ^{23}Na TPI images with TE=0.37-17 ms, TR=55 ms, NEX=4, in 4 min. of scan time per acquisition.

Spectra and Image Processing and Analysis

Magnetic resonance spectroscopy (MRS) data from the phantom experiments were processed for peak area measurements. Selected peaks from blood spectra were fitted in the frequency domain by fitting Lorentzian or Gaussian functions and the areas computed by integration.

Raw TPI data were reconstructed off-line on a Silicon Graphics (SGI) workstation using a regridding algorithm and 3D Fourier transformation described elsewhere [14].

To determine the T_{2f}, T_{2s} and image signal intensity as a function of MION amount, mean signal intensities were measured in multiple regions of interest (ROI) in sequentially acquired phantom and heart images (reconstructed at different TE values that ranged from 0.37-20 ms) with software developed previously [13]. T_{2f} and T_{2s} values were determined

EXPRESS MAIL NO. EL932684425US

Practitioner's Docket No. 56873 (71699) *PATENT*

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of: Chris D. Constantinides
For: **MAGNETIC RESONANCE IMAGING METHODS AND COMPOSITIONS**

the specification of which:

(check and complete (a), (b), or (c))

(a) ☐ is attached hereto.
(b) ☒ was filed on 1/10/02, as Application No. 10/044,296 and was amended on _____ *(if applicable)*.
(c) ☐ was described and claimed in International Application No. _____, filed on _____ and as amended on _____ *(if any)*.

STATEMENT OF FACTS IN SUPPORT OF FILING ON BEHALF OF NONSIGNING INVENTOR (37 C.F.R. SECTION 1.47)

NOTE: This statement as to the pertinent facts concerning the refusal of the nonsigning inventor to join in the application or where the nonsigning inventor cannot be found or reached must accompany the declaration signed on behalf of the nonsigning inventor by a joint inventor or by a legal representative who shows a proprietary interest. Where the entity with a proprietary interest executes the declaration on behalf of the nonsigning inventor there must also be a showing that such action is necessary to preserve the rights of the parties or to prevent irreparable damage. 37 C.F.R. 1.47(a) and (b).

This statement is made as to the exact facts that are relied upon to establish the diligent effort made to secure the execution of the declaration by the nonsigning inventor for the above identified patent application before deposit thereof in the Patent and Trademark Office.

(check next item, if applicable)

☒ Because signing on behalf of the nonsigning inventor is by a person or entity showing a sufficient proprietary interest, this statement also recites facts as to why this action was necessary to preserve the rights of the parties or to prevent irreparable damage.

This statement is being made by the available person having first-hand knowledge of the facts recited therein.

NOTE: The statement "must be signed, where at all possible, by a person having first-hand knowledge of the facts recited therein." M.P.E.P. section 409.03(d), 7th ed. If different persons have first-hand knowledge of different facts, then a declaration from each such person as to those facts he or she knows should be submitted separately.

NOTE: Copies of documentary evidence, such as certified mail return receipt, cover letter of instructions, telegrams, etc., that support a finding that the nonsigning inventor could not be reached should be made part of the affidavit or declaration. It is important that the affidavit or declaration contain statements of fact as apposed to conclusions. M.P.E.P. section 409.03(d), 7th ed.

IDENTIFICATION OF PERSON MAKING THIS STATEMENT OF FACTS

Peter F. Coreless

Name of person making statement

Address of person making statement

Edwards & Angell, LLP

101 Federal Street

Boston, MA 02110

LAST KNOWN ADDRESS OF THE NONSIGNING INVENTOR

NOTE: The last known address of the nonsigning inventor must be stated so that the PTO can forward the notice of filing of the application to the nonsigning inventor at said address. (37 C.F.R. section 1.47) A post office box is insufficient. M.P.E.P. section 409.03(e), 6th ed.

Chris D. Constantinides
Full name of nonsigning inventor

540 Elmcroft Boulevard, Apt. 2403
Rockville, MD 20850
Last known address of nonsigning inventor

NOTE: Ordinarily, the last known address will be the last known residence of the nonsigning inventor, but other addresses at which the nonsigning inventor may be reached should also be given in the space below. M.P.E.P. section 409.03(e), 6th ed.

DETAILS OF EFFORTS TO REACH NONSIGNING INVENTOR

NOTE: Complete either these facts or the facts as to REFUSAL OF NONSIGNING INVENTOR TO SIGN APPLICATION PAPERS.

NOTE: In addition to a recitation of these efforts, which must have been made before the application was deposited in PTO, copies of documentary evidence such as letters, telegrams, responses, etc. that support a finding that a nonsigning inventor could not be found or reached should, if available, be made part of the declaration. It is important that the affidavit or declaration contain statements of fact as opposed to M.P.E.P. section 409.03(d), 7th ed. conclusions.

Please see attached document: DETAILS OF REFUSAL OF NONSIGNING INVENTOR TO SIGN APPLICATION PAPERS

DETAILS OF REFUSAL OF NONSIGNING INVENTOR TO SIGN APPLICATION PAPERS

NOTE: Complete either these facts or the facts as to DETAILS OF EFFORTS TO REACH NONSIGNING INVENTOR.

NOTE: The circumstances of this refusal must be specified by the person to whom the refusal was made and, before a refusal can be alleged, it must be demonstrated that a bona fide attempt was made to present a copy of the application papers (specification, including claims, drawings and declaration) to the nonsigning inventor for signature. A copy of the application papers should be sent to the last known address of the nonsigning inventor, or, if the nonsigning inventor is represented by counsel, to the address of the nonsigning inventor's attorney. The time and place of an oral refusal should be stated, or a copy of the written refusal should be attached.

Where there is an express oral refusal, that fact along with the time and place of the refusal must be stated in the affidavit or declaration. When there is an express written refusal, a copy of the document evidencing that refusal must be made part of the affidavit or declaration.

If it is the conduct as a whole of the nonsigning inventor that is the refusal, then all the facts upon which this conclusion is based should be stated and a copy of any documentary evidence supporting these facts should be attached.

Where there is an express oral refusal, that fat along with the time and place of the e=refusal must be stated in the affidavit of declaration. When there is an express written refusal, a copy of the document evidencing that refusal must be made part of the affidavit or declaration.

Whenever the nonsigning inventor gives a reason for refusing to sign the application papers, that reason should be stated. M.P.E.P. section 409.03(d), 7th ed.

Please see attached document: DETAILS OF REFUSAL OF NONSIGNING INVENTOR TO SIGN APPLICATION PAPERS

PROOF OF NEED TO PREVENT IRREPARABLE DAMAGE OR PRESERVE THE RIGHTS OF THE PARTIES

*NOTE: This proof **must** be presented where the declaration is signed by a person with sufficient proprietary interest for the nonsigning inventor (37 C.F.R. section 1.47(b)), but is not a requirement when the person signing for the nonsigning inventor is a joint inventor. (37 C.F.R. section 1.47(a)).*

If a statutory bar is involved, the act or publication which is believed to constitute the bar should be identified. If a claim for priority is involved, the prior application or applications should be identified.

A diligent effort to prepare the application and obtain the inventor's signature thereon must be made, even if the application is being filed to avoid a bar or to claim priority. M.P.E.P. section 409.03(g), 7th ed.

Irreparable damage may be established by showing that a filing date is necessary to (1) avoid a statutory bar or (2) make a claim for priority, which should identify the prior application(s) involved.

Preservation of the rights of the parties may be demonstrated by a showing that the nonsigning inventor may reasonably be expected to enter into competition with the person having a proprietary interest and signing on behalf of the nonsigning inventor or that a firm plan for commercialization of the subject matter of the application has been adopted.

M.P.E.P. section 409.03(g), 7th ed.

The subject application claims priority from U.S. Provisional application Serial Number 60/260,524, filed January 10, 2001, one year prior to the filing of the subject application.

Docket No. 56873 (71699)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANT: Chris D. Constantinides

SERIAL NO.: 10/044,296 GROUP: Unknown

FILED: January 10, 2002 EXAMINER: Unknown

FOR: MAGNETIC RESONANCE IMAGING METHODS AND COMPOSITIONS

ASSISTANT COMMISSIONER FOR PATENTS
WASHINGTON, DC 20231

DETAILS OF REFUSAL OF NONSIGNING INVENTOR TO SIGN APPLICATION PAPERS

1. On January 10, 2002, the subject application was filed in the United States Patent and Trademark Office. The application was filed without a signed declaration and power of attorney.

2. On January 16, 2002, copies of the application, as filed, were mailed to the Johns Hopkins University Office of Technology Licensing, the assignee of the application.

3. On March 25, 2002, copies of the Official Filing Receipt, Notice to File Missing Parts of Nonprovisional Application, Declaration under 37 CFR 1.63 (Declaration) and Assignment were mailed to the Johns Hopkins University of Technology Licensing with a request that the signed Declaration form be obtained by that Office and provided to the undersigned, Peter Corless.

4. Peter Corless later telephoned the Johns Hopkins University Office of Technology Licensing (Johns Hopkins is the assignee of the application) to request that the signed Declaration form be returned for submission to the U.S. Patent and Trademark Office. Peter Corless was requested by the Johns Hopkins University Office of Technology Licensing to contact Mr. Constantinides directly to obtain his signature for the Declaration and Power for Attorney form.

5. Due to an unintentional docketing error, the final due date for filing the Response to Notice to File Missing Parts of Nonprovisional Application along with the signed Declaration form was docketed for a final response date of October 25, 2002 rather than September 25, 2002. That unintentional docketing error was first discovered after September 25, 2002.

7. Peter Corless attempted to contact Mr. Constantinides numerous times by phone and e-mail, without success. On October 18, 2002, counsel sent Mr. Constantinides a facsimile enclosing the Declaration form for his signature. Mr. Constantinides did not return the signed Declaration form. (See Exhibit A)

8. On October 24, 2002, Peter Corless again sent Mr. Constantinides a facsimile enclosing the Declaration form for his signature. Peter Corless requested that Mr. Constantinides return the signed document that same day. (See Exhibit B) Mr. Constantinides did not return the Declaration form.

9. On November 4, 2002, Mr. Constantinides sent Peter Corless a facsimile requesting that the documentation be sent to his home and that he would review the papers very carefully and reply in writing as soon as he could. (See Exhibit D)

10. In response to that November 4, 2002 facsimile from Mr. Constantinides, on November 4, 2002, Peter Corless sent Mr. Constantinides by both facsimile and Federal Express a further copy of the Declaration form for his signature as well as a copy of the application as filed with the U.S. Patent and Trademark Office. (See Exhibit C)

11. Thereafter, Peter Corless finally reached Mr. Constantinides by phone and requested that he sign the Declaration form. Mr. Constantinides replied that he wanted to study matters before signing the Declaration.

13. Peter Corless continued attempts to contact Mr. Constantinides by phone and e-mail to obtain the signed Declaration form.

14. On November 24, 2002, Mr. Constantinides replied to Peter Corless's numerous phone and email messages requesting return of the signed Declaration form. Mr. Constantinides indicated that he was currently reviewing the paperwork and that he would contact Peter Corless as soon as he completed review of the materials on hand. (See Exhibit E)

15. After Peter Corless informed the Johns Hopkins University Office of Technology Licensing of Mr. Constantinides refusal to provide the signed Declaration form, a representative of that Office of Technology Licensing contacted Mr. Constantinides by e-mail requesting that the signed Declaration be provided. Mr. Constantinides did not reply to that e-mail

16. To date, both Peter Corless and the Johns Hopkins Office of Technology Licensing have not received the signed Declaration and Power of Attorney. Further, counsel has not been given any indication by Mr. Constantinides that he intends to sign and return the Declaration and Power of Attorney.

Respectfully submitted,
JOHNS HOPKINS UNIVERSITY

Date: Dec. 20, 2002 By: _____

Peter F. Corless (Reg. No. 33,860)
EDWARDS & ANGELL, LLP
P.O. Box 9169
Boston, MA 02209
Tel. No. (617) 517-5512

Practitioner's Docket No. 56873 (71699) ***PATENT***

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of: Chris D. Constantinides
Application No.: 10/044,296 Group No.: 3737
Filed: 1/10/2002 Examiner: TBA
For: MAGNETIC RESONANCE IMAGING METHODS AND COMPOSITIONS

Assistant Commissioner for Patents
Washington, D.C. 20231
Box DAC

COMPLETION OF FILING REQUIREMENTS
-- NONPROVISIONAL APPLICATION

(check and complete this item, if applicable)

I. [X] This replies to the Notice to File Missing Parts of Application (PTO-1533) mailed February 25, 2002.

NOTE: If these papers are filed before the office letter issues, adequate identification of the original papers should be made, e.g., in addition to the name of the inventor and title of invention, the filing date based on the "Express Mail" procedure, the

CERTIFICATION UNDER 37 C.F.R. 1.10*

*(Express Mail label number is **mandatory**.)*
(Express Mail certification is optional.)

I hereby certify that this correspondence and the documents referred to as attached therein are being deposited with the United States Postal Service on this date **December 20, 2002**, in an envelope as "Express Mail Post Office to Addressee," mailing Label Number **EV932684425US** addressed to the: Assistant Commissioner for Patents, Washington, D.C. 20231.

(type or print name of person mailing paper)

Beth-Ann Marino
Signature of person mailing paper

WARNING: Certificate of mailing (first class) or facsimile transmission procedures of 37 C.F.R. 1.8 cannot be used to obtain a date of mailing or transmission for this correspondence.

WARNING: Each paper or fee filed by "Express Mail" **must have the number of the "Express Mail" mailing label placed thereon prior to mailing. 37 C.F.R. 1.10(b).*
*"Since the filing of correspondence under § 1.10 without the Express Mail mailing label thereon is an oversight that can be avoided by the exercise of reasonable care, requests for waiver of this requirement will **not** be granted on petition." Notice of Oct. 24, 1996, 60 Fed. Reg. 56,439, at 56,442*

serial number from the return post card or the attorney's docket number added.

[X] A copy of the Notice to File Missing Parts of Application--Filing Date Granted (Form PTO-1533) is enclosed.

NOTE: The PTO requires that a copy of Form PTO-1533 be returned with the response to the notice to file missing parts to the application.

DECLARATION OR OATH

II. [X] No declaration or oath was filed. Enclosed is the original declaration or oath for this application.

NOTE: If the correct inventor or inventors are not named on filing a nonprovisional application under Section 1.53(b) without an executed oath or declaration under Section 1.63, the later submission of an executed oath or declaration under Section 1.63 during the pendency of the application will act to correct the earlier identification of inventorship. 37 C.F.R. Section 1.48(f)(1).

OR

[ ] The declaration or oath that was filed was determined to be defective. A new original oath or declaration is attached.

NOTE: For surcharge fee for filing declaration after filing date complete item VI(3) below.

NOTE: "The following combinations of information supplied in an oath or declaration filed after the filing date are acceptable as minimums for identifying a specification and compliance with any one of the items below will be accepted as complying with the identification requirement of 37 C.F.R. Section 1.63:

(A) application number (consisting of the series code and the serial number, e.g., 08/123,456);

(B) serial number and filing date;

(C) attorney docket number which was on the specification as filed;

(D) title which was on the specification as filed and reference to an attached specification which is both attached to the oath or declaration at the time of execution and submitted with the oath or declaration; or

(E) title which was on the specification as filed and accompanied by a cover letter accurately identifying the application for which it was intended by either the application number (consisting of the series code and the serial number, e.g., 08/123,456), or serial number and filing date. Absent any statement(s) to the contrary, it will be presumed that the application filed in the PTO is the application which the inventor(s) executed by signing the oath or declaration.

M.P.E.P. Section 601.01(a), 7th ed.

NOTE: Another minimum found acceptable in the declaration is the filing date (i.e., date of express mail) and the express mail number, useful where the serial number is not yet known. But note the practice where the express mail deposit is a Saturday, Sunday or holiday within the District of Columbia. 37 C.F.R. Section 1.10(c).

(complete (c) or (d), if applicable)

Attached is a

(c) [ ] Statement by a registered attorney that the application filed in the PTO is the application that the inventor executed by signing the declaration.

(d) [ ] Statement that the "attached" specification is a copy of the specification and any amendments

thereto that were filed in the PTO to obtain the filing date.

(e) [X] Petition Under 37 C.F.R. § 1.47, Petition for Revival of an Application for Patent Abandoned Unintentionally, Statement of Facts in Support of Filing on Behalf of Non-Signing Inventor, together with Exhibits (A-D.) and Proof of Proprietary Interest.

AMENDMENT CANCELLING CLAIMS

III. [ ] Cancel claims _____ inclusive.

TRANSMITTAL OF ENGLISH TRANSLATION OF NON-ENGLISH LANGUAGE PAPERS

IV. [ ] Submitted herewith is an English translation of the non-English language application papers as originally filed. Also submitted herewith is a statement by the translator of the accuracy of the translation. It is requested that this translation be used as the copy for examination purposes in the PTO.

NOTE: For fee processing a non-English application, complete item VI(5) below.

NOTE: A non-English oath or declaration in the form provided or approved by the PTO need not be translated. 37 C.F.R. Section 1.69(b).

NOTE: The translation for a regular application filed in a foreign language must be verified. 37 C.F.R. Section 1.52(d).

SMALL ENTITY STATUS

V. [ ] A statement that this filing is by a small entity

(check and complete applicable items)

[ ] is attached.

[ ] A separate refund request accompanies this paper.

[ ] was filed on _____ (original).

COMPLETION FEES

VI.

WARNING: *Failure to submit the surcharge fees where required will cause the application to become abandoned. 37 C.F.R. Section 1.53.*

NOTE: For effect on fees of failure to establish status, or change status, as a small entity, see 37 C.F.R. Section 1.28(a).

1. Filing fee

[X] original patent application
(37 C.F.R. Section 1.16(a)--$740.00: small entity--$370) $ 740.00

[ ] design application
(37 C.F.R. Section 1.16(f)--$330; small entity--$165) $

2. Fees for claims

[ ] each independent claim in excess of 3
(37 C.F.R. Section 1.16(b)--$84; small entity--$42) $

[X] each claim in excess of 20
(37 C.F.R. Section 1.16(c)--$18; small entity--$9) $ 342.00

[X] multiple dependent claim(s)
(37 C.F.R. Section 1.16(d)--$280: small entity--$140) $ 280.00

3. Surcharge fees

[X] late payment of filing fee and/or late filing of original declaration or oath
(37 C.F.R. Section 1.16(e)--$130; small entity--$65)$ 130.00

NOTE: Even where a facsimile declaration or oath signed by the inventor(s) was part of the originally filed papers, the surcharge fee is required.

NOTE: If both the filing fee and declaration or oath were missing from the original papers, the Office practice under 37 C.F.R. Section 1.16(e) is that only one surcharge fee need be paid whether the later filed oath or declaration and/or the filing fee are submitted afterwards at the same time or at different times.

4. [ ] Petition and fee for filing by other than
all the inventors or a person not the inventor
(37 C.F.R. Sections 1.17(i) and 1.47--$130)$

5. [ ] Fee for processing an application filed with
a specification in a non-English language
(37 C.F.R. Sections 1.17(k) and 1.52(d)--$130) $

6. [ ] Fee for processing and retention of application
(37 C.F.R. Sections 1.21(l) and 1.53(d)--$130) $

NOTE: 37 C.F.R. Section 1.21(l) establishes a fee for processing and retaining any application which is abandoned for failing to complete the application pursuant to 37 C.F.R. Section 1.53(f) and this, as well as, the changes to 37 C.F.R. Section 1.53 and 1.78 indicate that in order to obtain the benefit of a prior U.S. application, either the basic filing fee or the processing

and retention fee of Section 1.21(l) within 1 year of notification under Section 1.53(f) must be paid.

7. [ ] Assignment (See "ASSIGNMENT COVER SHEET") $

Total completion fees $ 1,492.00

EXTENSION OF TIME

VII.

(complete (a) or (b), as applicable)

The proceedings herein are for a patent application, and the provisions of 37 C.F.R. Section 1.136(a) apply.

(a) [ ] Applicant petitions for an extension of time, the fees for which are set out in 37 C.F.R. Section 1.17(a)(1)-(4), for the total number of months checked below:

Extension (months)	Fee for other than small entity	Fee for small entity
[ ] one month	$110	$55
[ ] two months	$400	$200
[ ] three months	$920	$460
[ ] four months	$1,440	$720

Fee $

If an additional extension of time is required, please consider this a petition therefor.

(check and complete the next item, if applicable)

[ ] An extension for _____ months has already been secured, and the fee paid therefor of $ is deducted from the total fee due for the total months of extension now requested.

Extension fee due with this request $

OR

(b) [ ] Applicant believes that no extension of term is required. However, this conditional petition is being made to provide for the possibility that applicant has inadvertently overlooked the need for a petition and fee for extension of time.

TOTAL FEE DUE

VIII.

The total fee due is $1,492.00

Completion fee(s) $
Extension fee (if any) $

Total Fee Due $ 1,492.00

PAYMENT OF FEES

IX.

[ ] Enclosed is a check in the amount of $ _____.

[X] Charge Account No. 04-1105 in the amount of $ 1,492.00.
A duplicate of this request is attached.

NOTE: Fees should be itemized in such a manner that it is clear for which purpose the fees are paid. 37 C.F.R. Section 1.22(b).

Please change Account No. $1,492.00 for any fees which may be due by this paper.

AUTHORIZATION TO CHARGE ADDITIONAL FEES

X.

WARNING: Accurately count claims, especially multiple dependent claims, to avoid unexpected high charges if extra claims are authorized.

NOTE: "Amounts of twenty-five dollars or less will not be returned unless specifically requested within a reasonable time, nor will the payer be notified of such amounts; amounts over twenty-five dollars may be returned by check or, if requested, by credit to a deposit account." 37 C.F.R. Section 1.26(a).

[X] The Commissioner is hereby authorized to charge the following additional fees that may be required by this paper and during the pendency of this application to Account No. 04-1105 _____.

[X] 37 C.F.R. Section 1.16(a), (f) or (g) (filing fees)
[X] 37 C.F.R. Section 1.16(b), (c) and (d) (presentation of extra claims)

NOTE: Because additional fees for excess or multiple dependent claims not paid on filing or on later presentation must only be paid or these claims cancelled by amendment prior to the expiration of the time period set for response by the PTO in any notice of fee deficiency (37 C.F.R. Section 1.16(d)), it might be best not to authorize the PTO to charge additional claim fees, except possibly when dealing with amendments after final action.

[X] 37 C.F.R. Section 1.16(e) (surcharge for filing the basic filing fee and/or declaration on a date later than the filing date of the application)
[X] 37 C.F.R. Section 1.17(a)(1)-(5)(extension fees pursuant to Section 1.136(a).
[X] 37 C.F.R. Section 1.17 (application processing fees)

NOTE: "A written request may be submitted in an application that is an authorization to treat any concurrent or future reply, requiring a petition for an extension of time under this paragraph for its timely submission, as incorporating a petition for extension of time for the appropriate length of time. An authorization to charge all required fees, fees under Section 1.17, or all required extension of time fees will be treated as a constructive petition for an extension of time in any concurrent or future reply requiring a petition for an extension of time under this paragraph for its timely submission. Submission of the fee set forth in Section 1.17(a) will also be treated as a constructive petition for an extension of time in any concurrent reply requiring a petition for an extension of time under this paragraph for its timely submission." 37 C.F.R. Section 1.136(a)(3).

[ ] 37 C.F.R. Section 1.18 (issue fee at or before mailing of Notice of Allowance, pursuant to 37 C.F.R. Section 1.311(b))

NOTE: Where an authorization to charge the issue fee to a deposit account has been filed before the mailing of a Notice of Allowance, the issue fee will be automatically charged to the deposit account at the time of mailing the notice of allowance. 37 C.F.R. Section 1.311(b).

NOTE: 37 C.F.R. Section 1.28(b) requires "Notification of any change in loss of entitlement to small entity status must be filed in the application . . . prior to paying, or at the time of paying . . . issue fee . . ." From the wording of 37 C.F.R. Section 1.28(b): (a) notification of change of status must be made even if the fee is paid as "other than a small entity" and (b) no notification is required if the change is to another small entity.

SIGNATURE OF PRACTITIONER

Reg. No.: 33,860

Peter F. Corless
(type or print name of practitioner)

Tel. No.: (617) 523-3400

EDWARDS & ANGELL, LLP
P.O. Box 9169
Boston, MA 02209
P.O. Address

Customer No.: 21874

BOS2_322063.1